ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Li, M. J. Lear and Y. Hayashi, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC03191F.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ROYAL SOCIETY OF CHEMISTRY
View Article Online
DOI: 10.1039/C8CC03191F

Journal Name

COMMUNICATION

Autoinductive Conversion of α,α-Diiodonitroalkanes to Amides and Esters Catalysed by Iodine Byproducts under O_2

Jing Li, [a] Martin J. Lear* [b] and Yujiro Hayashi* [a]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Studies to convert nitroalkanes into amides and esters using I_2 and O_2 revealed *in situ*-generated iodine species facilitate the homolytic C–I bond cleavage of α,α-diiodonitroalkanes, arguably in an autoinductive or autocatalytic manner. Consequently, we devised a rapid and economical I_2/O_2-based method to synthesise sterically hindered esters directly from primary nitroalkanes.

It is not trivial to decipher the most meaningful and productive pathway within a multistep reaction process.[1] A case in point comes from our studies to transform primary nitroalkanes **1** directly into amides **4** in the presence of I_2, O_2, bases, and nucleophilic amines (Figure 1a; HNu = HNR'R'').[2–4] From these studies, we found the doubly α-iodinated derivative **2** of the nitroalkane **1** to be key to the oxidative process.[2b] In contrast to mechanisms involving the α-amination of α-bromonitroalkanes with electrophilic *N*-iodinated amines,[5] we have proposed the amide product **4** is generated by nucleophilic amine attack on the acyl derivative **3**, as derived by addition of O_2 onto **2** through the homolytic cleavage of C–I bonds.[2b]

Clearly the acyl derivative **3** can also react with other nucleophiles, such as residual water to form carboxylic acids and alcohols to form esters. Indeed, we have previously isolated carboxylic acids **4** (HNu = HOH) as side-products.[2] If made synthetically useful under mild conditions with less nucleophilic amines or alcohols, we could expand the one-pot transformation of nitroalkanes into other useful functionalities.[6] Herein, we detail our mechanistic development of oxidatively converting primary nitroalkanes **1**, via α,α-diiodonitroalkanes **2** under O_2, into sterically congested esters **4** (HNu = HOR'). This method was achieved by realising that the rate-limiting step during the conversion of **2** to **3** is autoinduced by the iodine byproducts derived from **2** itself (Fig. 1(b)).[7]

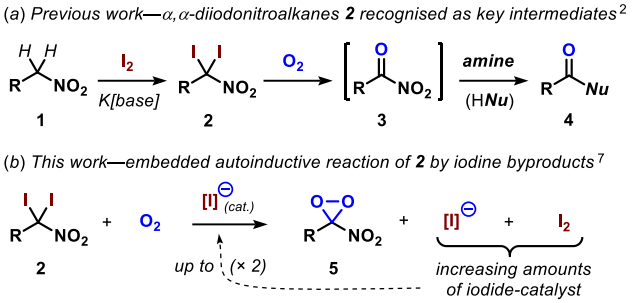


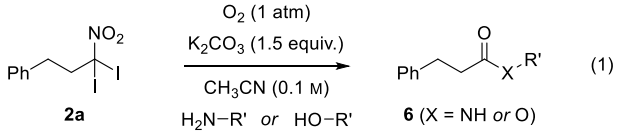
Fig. 1 Proposed oxidative conversion of (*a*) nitroalkanes **1** to acyl derivatives **3** and **4** *via* the (*b*) autoinductive reaction of the nitro-diiodide intermediate **2** with increasing concentrations of catalytically-active iodide byproducts derived from **2** and I_2.[2,7]

Most strikingly, the reactions from **2a** to **6** (Eq. (1)) with relatively weak nucleophiles (CH_3OH, $CF_3CH_2NH_2$) displayed clear sigmoidal kinetic profiles at room temperature on the NMR timescale (Fig. 2, red and black curves). In contrast, the initial reaction between **2a** and benzylamine proceeded exponentially with no slow induction period at room temperature, whereas an uncommon sigmoidal profile was observed at –10 °C (Fig. 2, cyan and blue curves). Several mechanistic reasons can be attributed to causing such sigmoidal kinetic profiles: For instance, the final product, an intermediate-product, a byproduct or a side-product of the reaction could be accelerating a rate-determining step in a chain-like, cross-catalytic, autoinductive or autocatalytic fashion.[7] We thus decided to study the oxidative conversion of the α,α-diiodonitroalkane **2a** to the carboxylic derivatives **7**/**8** systematically and quantify the kinetic effects of adding each identifiable reaction product at 20 mol% by ^{1}H NMR analysis (Eq. (2), Figure 3).

In the first instance, without any additives, the methyl ester **7** and carboxylic acid **8** were isolated in 75% and 25% yield, respectively, and characterized by ^{1}H NMR (Eq. (2)). This reaction under standard conditions also produced nitrite salts (KNO_2)[2b] and I_2 crystals as byproducts, as detected by ion chromatography and observed after solvent removal. Next, we

[a] Department of Chemistry, Graduate School of Science, Tohoku University, Aza Aramaki, Aoba-ku, Sendai 980-8578, Japan. E-mail: yhayashi@m.tohoku.ac.jp
[b] School of Chemistry, Brayford Pool, University of Lincoln, Lincoln LN6 7TS, United Kingdom. E-mail: mlear@lincoln.ac.uk
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

monitored the effect of adding each reaction product at the start of the reaction, including the ester **7**, carboxylate **8**, nitrite and hydrogen carbonate salts (Fig. 3(a)). All these cases displayed sigmoidal kinetic profiles similar to the reaction with no additives, although small variations in initial induction times were observed.



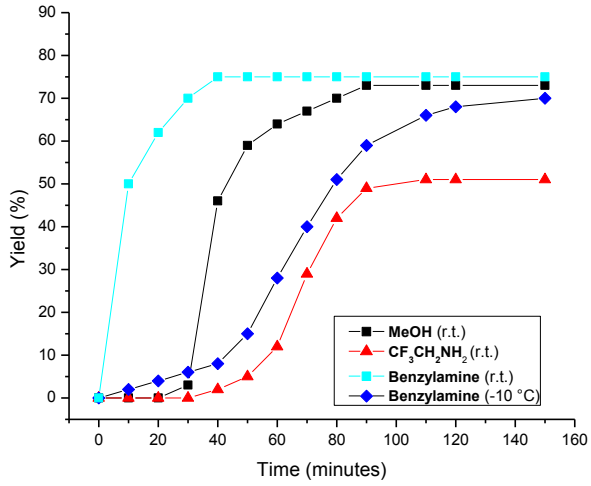
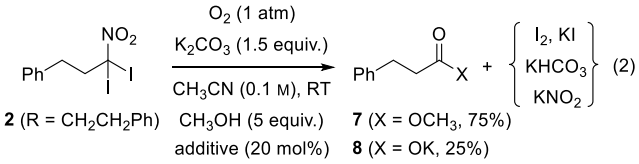


Fig.2 ^{1}H NMR profiles of α,α-diiodonitroalkane **2a** reacting with MeOH (5 equiv.) or an amine (1.5 equiv.) to form product **6** according to Eq. (1).

Eventually, I_2 was selected as an additive to the reaction (Eq. (2); Fig. 3(b)). This gave a dramatic improvement in the initial reaction rate, similar to conventional pseudo-first-order kinetic profiles (Fig. 3(a), red curve). Here the addition of I_2 gave a sustained purple-red colour throughout the course of the reaction. In comparison, without pre-adding I_2, the reaction turned from yellow to a similar purple-red colour after 30 minutes, at which time the rapid formation of the ester product **7** was clearly observed (Fig. 3(a), black curve). The effect of I_2 was therefore studied in more detail by monitoring the *in situ* consumption of the α,α-diidonitroalkane **2a** and the *in situ* formation of ester **7** by React-IR (Fig. 3(b)). Again, we followed the standard reaction without any additives (Eq. (2)) and, although the IR-data were consistent with our initial ^{1}H NMR analysis, the 0–40 min induction periods were better resolved (*cf.* Fig. 3(a), black curve; Fig. 3(b), blue curve). Addition of I_2 also gave a similar conventional kinetic profile to our ^{1}H NMR analysis, which produced the desired ester **7** within 80 min (cf. Fig. 3(a) and Fig. 3(b), red curves).

Since I_2 can act as a dual source of cationic iodonium species (I^+) and anionic iodide species (I_3^- or I^-) in solution,[8] we performed separate reactions either by adding 20 mol% of NIS as an I^+ source or by adding 20 mol% of NEt_4I as an I^- source. While NIS demonstrated a slight retardation on the initial reaction rate (*cf.* Fig. 3(b), purple and blue curves), NEt_4I dramatically accelerated the overall reaction rate and gave no observable induction period (Fig. 3(b), blue curve). Furthermore, a similar iodide-mediated acceleration effect was observed in the case of $CF_3CH_2NH_2$ reacting with **2a** to form the amide **6** (XR' = $NHCH_2CF_3$; see ESI†). Collectively, these data support iodide byproducts (I_n^-) as the principal species which catalyse the oxidative conversion of the diiodide **2a** to the ester **7** under O_2.



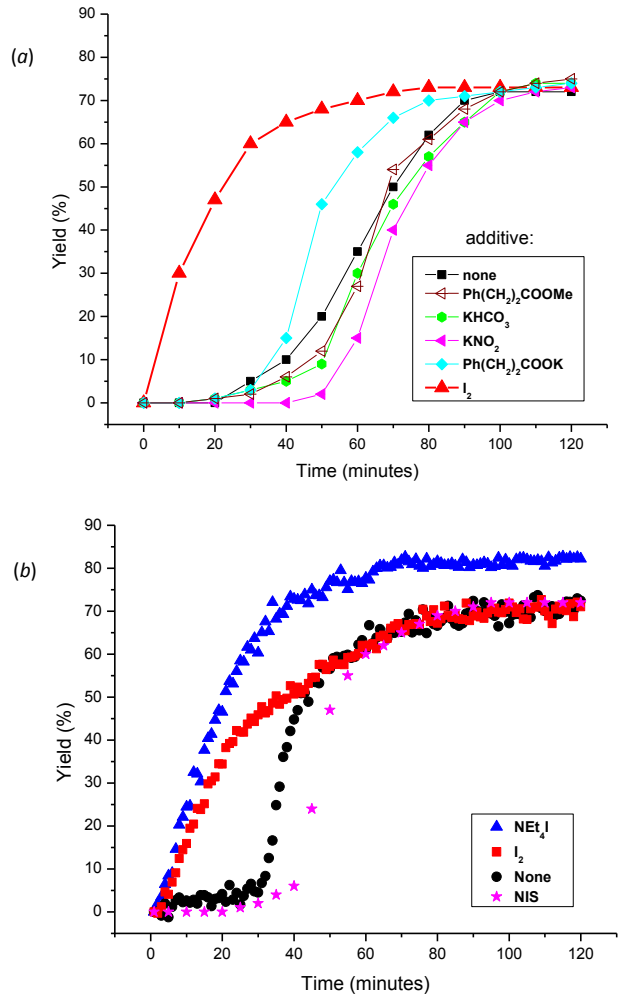
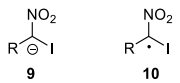
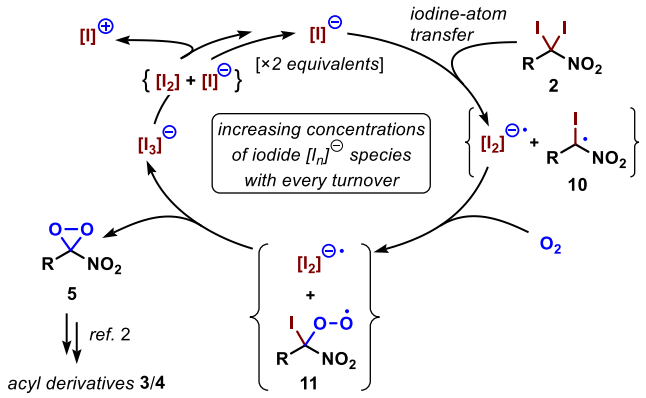


Fig. 3 Normalised profiles of α,α-diiodonitroalkane **2a** reacting with MeOH (5 equiv.) to form methyl ester **7** according to Eq. (2): (*a*) ^{1}H NMR analysis with various reaction product additives (20 mol%); (*b*) React-FT-IR analysis with various iodine sources (20 mol%), except NMR was used for NIS.



The mechanistic implications of these findings are thought provoking, especially when we take related studies into account.[2,4,5] Several mechanistic observations are worth noting: (1) From previously reported radical clock experiments, the

radical **10** is an evidenced key intermediate in this process.[2b] (2) The direct reaction of O_2 to generate the radical **10** from an α-iodo, α-nitro, α-carbanion **9**, which can conceivably be formed by ionic attack of an iodide anion or another nucleophile onto an α,α-diiodonitroalkane **2**, can be ruled out from our previous experiments.[2b] (3) The reaction remains unaffected by light exposure, which indicates that the homolytic cleavage of the carbon-iodine bond of **2** via photo-activation can be ruled out. (4) Experiments with the addition of relatively non-nucleophilic radical initiators (e.g., $(PhCO)_2O_2$ or AIBN at 50 °C) or radical inhibitors (e.g. TEMPO at 25 °C) were found to not alter the induction periods under our reaction conditions and substrates. Such additive effects would be expected to be significant for radical chain reactions, but not for iodine-atom transfer reactions (see ESI†).[7d]



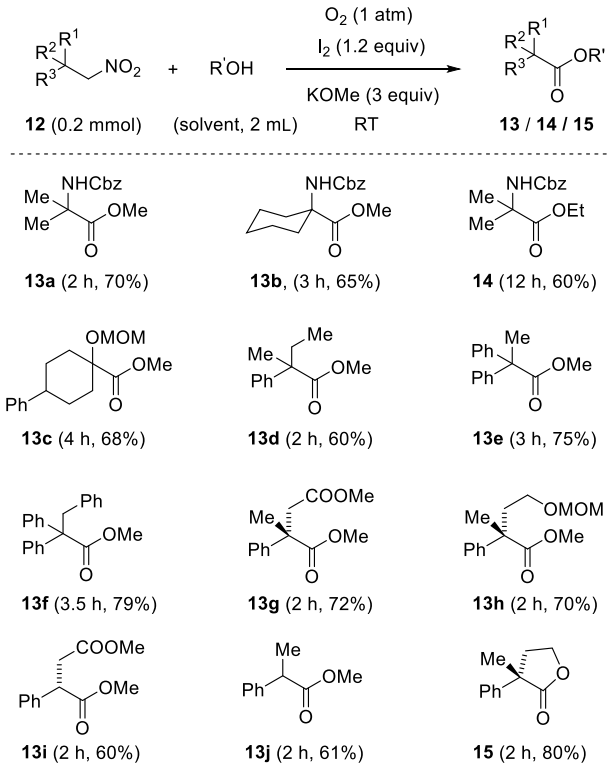
Scheme 1. Proposed autoinduction of α,α-diiodonitroalkanes **2** by virtue of increasing concentrations of catalytically active iodide species (I_n^-).[2,7–13]

Based on these results, our autoinductive interpretation between the α,α-diiodonitroalkane **2**[2b] and iodine byproducts (Fig. 1(b)) is presented in Scheme 1. As iodide anions (I_n^-) are known to be good electron donors and can afford alkyl radicals from alkyl iodides,[9–12] it is reasonable to expect iodine-atom transfer from the more highly electron deficient α,α-diiodonitroalkane **2** to I^-. This process would give a putative diiodide radical anion ($I_2^{\bullet-}$) and the previously evidenced carbon radical **10**[2b] (Scheme 1). The subsequent reaction of carbon radical **10** with oxygen would be similar to the mechanism we established during the oxidative Nef reaction of nitroalkanes with molecular oxygen.[3b] That is, the radical **10** reacts with O_2 to generate the peroxy-adduct **11**,[12] which would provide the dioxirane **5**.[2,3b,4] The $I_2^{\bullet-}$ byproduct can then couple homogenically with mono-iodine ($I^\bullet$) to generate I_3^- as a known source of I_2 and I^-.[8] Latterly, in addition to our previous proposal,[2a] dioxiranes **5** can also conceivably transform to the acyl derivative **3** through the action of I^- anions.[13]

Under this mechanistic framework, the observed autoinduction profiles of Fig. 2 and Fig. 3 would be explained as follows: As diiodine (I_2) is also a source of electrophilic mono-iodine (I^+) and an extra equivalent of anionic mono-iodide (I^-),[8] the iodide byproducts of **2** can increase up to two-equivalents during every turn of this cycle, making the reaction autoinductive (cf. Fig. 1(b) and Scheme 1).[7–13] The initial absence of I_n^- species thus accounts for the observed 30–40 minute induction periods (cf. Fig. 2 and Fig. 3). Iodide can be generated, however, through alternative reaction pathways, for example, through a slow C–NO_2→C–ONO homogenic rearrangement, C–I homolytic bond cleavage, or by nucleophilic attack on the *gem*-diiodide **2**.[2,5]

To provide evidence of possible nucleophilic attack on **2** releasing iodide, the differing kinetic profiles of benzylamine at room temperature and –10 °C were studied in more detail (see Fig. 2). Firstly, the addition of 20 mol% of NEt_4I for the reaction at –10 °C (cf. Eq. (1)) exhibited a conventional kinetic profile with no induction period—see ESI† for comparative reaction profiles of benzylamine in CD_3CN by ^1H NMR analysis. Secondly, without iodide additives at room temperature, ^1H NMR experiments showed that benzylamine forms an amine halogen bonded complex with **2a** and a mono α-iodinated derivative **9**, as well as benzaldehyde after work up (see ESI†). Thirdly, the same amine complex of **2a** was also observed at –10 °C, but deiodinated **2a** and benzaldehyde were not detected. Collectively, this evidence indicates **2a** can transfer an iodine to the amino group of benzylamine at room temperature, which likely results in imine formation and the release of iodide catalyst. In further support of the need to release iodide, we also observed the accelerating effect of adding strong nucleophiles such as PPh_3 and SMe_2 (see ESI†). Indeed, under unfavorable conditions with weak nucelophiles, the α,α-diiodonitroalkane **2a** is suggested to produce iodide byproducts relatively slowly.[2b] Reactions with methanol at room temperature or benzylamine at –10 °C thus necessitate the gradual generation of iodide anions in sufficient concentrations to catalyse the formation of the radical **10** from **2a**, as reflected in their kinetic profiles (cf. Scheme 1, Fig. 2 and Fig. 3).

On the mechanistic basis of iodide-mediated autoinduction, we thus decided to explore the direct oxidative esterification between primary nitroalkanes and primary alcohols with a slight excess of I_2 (1.2 equiv.) under a variety of basic conditions (see Scheme 2 and ESI† for optimization studies). Compared to conventional methods, which first convert primary nitroalkanes to carboxylic acids before ester formation,[14] our aim was to develop a one-pot method to directly make sterically challenging esters *via in situ* α,α-diiodonitroalkanes **2** from readily prepared, but hindered primary nitroalkanes **12** (Scheme 2).[6] Here, 1.2 equivalents of I_2 were considered to be sufficient because I^- would oxidise to I^+ under O_2, as reported previously.[2b] Thus I_2 was chosen to act as a source of iodonium cations to not only form **2**, but also to form iodide byproducts to facilitate the homolytic cleavage of **2** to the O_2-reactive carbon-radical **10** (cf. Scheme 1).[8] Experimentally, the α-amino, α-hydroxy, α-alkyl, α-benzyl or α-phenyl functionalized α,α,α-trisubstituted methyl esters **13a–f** all formed in good yields in a direct and rapid manner (Scheme 2). Although an increase in the bulkiness of the β-position of the starting nitroalkane gave slightly longer reaction times, the yields remained good (cf. **13d–f**). Conveniently, the α-chiral trisubstituted esters **13g/h** and γ-lactone **15** can be prepared in high enantioslectivity from chiral nitroalkanes via the asymmetric organocatalysed Michael reaction of nitromethane with β,β-disubstituted α,β-enals.[15]



Scheme 2. Oxidative esterification and lactonisation of readily prepared primary nitroalkanes into sterically congested methyl or ethyl esters.

In summary, the direct aerobic conversion of α,α-diiodonitroalkanes **2** to amides or esters with relatively weak nucleophiles was found to display unusual sigmoidal reaction profiles, as evidenced by quantitative ^{1}H NMR and React-IR studies (Fig. 3). Systematic addition of sub-stoichiometric amounts of potential products derived from **2** (Eq. (2)) clearly identified mono-iodide anions to accelerate the reaction. Due to the increasing generation of up to two-equivalents of iodine byproducts after each catalytic cycle,[8] we herein propose a new case of autoinduction,[7] whereby the iodide-mediated formation of O_2-reactive carbon radicals **10** from **2** is reasoned to occur through an iodine-atom transfer event (Scheme 1).[11] Under this mechanistic framework, we developed a convenient one-pot oxidative transformation of readily prepared β,β,β-trisubstituted nitroalkanes[15] into sterically encumbered α,α,α-trisubstituted esters, which are difficult to access directly by conventional methods.[14] Application of these fundamental understandings[7–13] to useful metal-free and iodine-based oxidative transformations are ongoing.[2–6]

We thank Mr. Yuki Haro of *Mettler-Teledo K.K.* for providing React-IR analysis support and equipment. We also thank Professor E. Kwon of Tohoku University, Japan, for X-ray data analysis and support. This work was funded by JSPS KAKENHI Grant Number JP 16K13942.

Conflicts of interest

There are no conflicts to declare.

Notes and references

View Article Online
DOI: 10.1039/C8CC03191F

1 Perspectives on deciphering organic reaction mechanisms: (*a*) D. G. Blackmond, *Angew. Chem. Int. Ed.*, 2005, **44**, 4302–4320; (*b*) D. G. Blackmond, *J. Am. Chem. Soc.*, 2015, **137**, 10852–10866; (*c*) G.-J. Cheng, X. Zhang, L. W. Chung, L. Xu, and Y.-D. Wu, *J. Am. Chem. Soc.*, 2015, **137**, 1706–1725.

2 (*a*) J. Li, M. J. Lear, Y. Kawamoto, S. Umemiya, A. Wong, E. Kwon, I. Sato and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2015, **54**, 12986–12990; (*b*) J. Li, M. J. Lear, E. Kwon and Y. Hayashi, *Chem. Eur. J.*, 2016, **22**, 5538–5542.

3 (*a*) Y. Hayashi and S. Umemiya, *Angew. Chem. Int. Ed.*, 2013, **52**, 3450–3452; (*b*) S. Umemiya, K. Nishino, I. Sato and Y. Hayashi, *Chem. Eur. J.*, 2014, **20**, 15753–15759.

4 Challenging O_2-mediated amidations of 1,1-dicyanoalkanes via dioxiranes and acyl cyanides: J. Li, M. J. Lear and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2016, **55**, 9060–9064.

5 For umpolung amidation mechanisms via putative *N*-iodo amines, see: (*a*) B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027–1032; (*b*) Shackleford, J. P.; Shen, B.; Johnston, J. N. Proc. Natl. Acad. Sci. USA 2012, 109, 44–46; (*c*) K. E. Schwieter, B. Shen, J. P. Shackleford, M. W. Leighty, J. N. Johnston, *Org. Lett.*, 2014, **16**, 4714–4717.

6 Classical and emerging uses of nitroalkanes in synthesis: (*a*) D. Seebach, E. W. Colvin, F. Lehr and T. Weller, *Chimia*, 1979, **33**, 1–18; (*b*) A. G. M. Barrett, D. Dhanak, G. G. Graboski and S. J. Taylor, *Organic Synthesis*, 1989, **68**, 8–13; (*c*) N. Ono, The Nitro Group in Organic Synthesis, Wiley-VCH, New York, 2001; (*d*) R. Ballini and M. Petrini, *Tetrahedron*, 2004, **60**, 1017–1047; (*e*) M. W. Leighty, J. P. Shackleford, B. Shen and J. N. Johnston, *Proc. Natl. Acad. Sci. USA*, 2012, **109**, 44–46.

7 Such reactions can be argued to be autoinductive or autocatalytic. For leading perspectives in catalysis, see: (*a*) D. G. Blackmond, *Angew. Chem. Int. Ed.*, 2009, **48**, 386–390; (*b*) A. J. Bissette and S. P. Fletcher, *Angew. Chem. Int. Ed.*, 2013, **52**, 12800–12826; (*c*) M. P. Mower and D. G. Blackmond, *J. Am. Chem. Soc.*, 2015, **137**, 2386–2391; (*d*) A. Studer and D. P. Curran, *Angew. Chem. Int. Ed.*, 2016, **55**, 58–102.

8 Extensive equilibria can occur between I_2, I^- and I_3^- in solution. Alternative $[I_n]^-$ species are thus conceivable catalysts: (*a*) R. L. Benoit, M. F. Wilson and S.-Y. Lam, *Can. J. Chem.*, 1977, **55**, 792–797; (*b*) J. M. Gardner, M. Abrahamsson, B. H. Farnum and G. J. Meyer, *J. Am. Chem. Soc*., 2009, **131**, 16206–16214; (c) L. Li, W. B. Liu, H. Y. Zeng, X. Y. Mu, G. Cosa, Z. T. Mi and C.-J. Li, *J. Am.* Chem. Soc., 2015, **137**, 8328–8331.

9 Oxidation of iodide to iodine in the presence of O_2: A. B. Couto, D. Cassoli de Souza, E. R. Sartori, P. Jacob, D. Klockow and E. A. Neves, *Anal. Lett*., 2006, **39**, 2763–2774.

10 Iodide catalysed C–I bond cleavage in polymer synthesis: A. Goto, A. Ohtsuki, H. Ohfuji, M. Tanishima and H. Kaji, *J. Am. Chem. Soc.*, 2013, **135**, 11131–11139.

11 N. Zhang, S. R. Samanta, B. M. Rosen and V. Percec, *Chem. Rev.*, 2014, **114**, 5848–5958.

12 Peroxy-adduct generation from dihaloalkanes: (*a*) J. M. Beames, F. Liu, L. Lu, M. I. Lester, *J. Am. Chem. Soc.*, 2012, **134**, 20045–20048; (*b*) X. Ge, K. L. M. Hoang, M. L. Leow and X.-W. Liu, *RSC Adv*., 2014, **4**, 45191–45197.

13 Iodide and superoxide can reduce dioxiranes to ketones: W. Adam, G. Asensio, R. Curci, M. E. González-Núñez, R. Mello, *J. Am. Chem. Soc.*, 1992, **114**, 8345–8349.

14 (*a*) N. Kornblum and P. A. Wade, *J. Org. Chem.*, 1973, **38**, 1418–1420; (*b*) C. Matt, A. Wagner and C. Mioskowski, *J. Org. Chem.*, 1997, **62**, 234–235.

15 Y. Hayashi, Y. Kawamoto, M. Honada, D. Okamura, S. Umemiya, Y. Noguchi, T. Mukaiyama and I. Sato, *Chem. Eur. J.*, 2014, **38**, 12072–12082.